Title: Factor V Leiden Thrombophilia *GeneReview* Supplemental Information: History
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Note: The following information was provided by the author listed above and has not been reviewed by *GeneReviews* staff.

Haplotype analysis of the factor V gene strongly suggests that the variant at nucleotide 1691 was a single event that occurred 20,000-30,000 years ago, after the evolutionary separation of whites from Asians and Africans [Zivelin et al 1997]. The high prevalence of factor V Leiden among whites suggests a balanced polymorphism with some type of survival advantage associated with the heterozygous state. Some investigators speculate that the mild hypercoagulable state conferred by the variant could have had a beneficial effect in reducing mortality from bleeding associated with childbirth or trauma in pre-modern times [Zivelin et al 1997, Dahlbäck 2008]. One retrospective study reported a significantly reduced risk for intrapartum bleeding complications in women heterozygous for factor V Leiden compared to women without the variant [Lindqvist et al 1998]. Factor V Leiden heterozygotes undergoing elective cardiac surgery had significantly less blood loss and a lower risk of requiring a blood transfusion than individuals with a normal factor V genotype [Donahue et al 2003]. Another study suggested that the variant is associated with a fivefold lower risk for spontaneous intracranial hemorrhage, consistent with the proposed protective effect [Corral et al 2001]. A study of women who had successful in vitro fertilization suggested that factor V Leiden enhances embryo implantation, thereby favoring the early survival of heterozygotes [Gopel et al 2001]. Analysis of a large randomized trial of individuals with severe sepsis showed that factor V Leiden heterozygotes had a threefold greater probability of survival, confirming animal models of sepsis that suggest a similar survival benefit [Kerlin et al 2003]. Although each of these hypothesized beneficial effects could account for the persistence of the variant, a survival advantage remains to be confirmed.

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